PROPUBLICA

Use Only as Directed

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During the last decade, more than 1,500 Americans died after accidentally taking too much of a drug renowned for its safety: acetaminophen, one of the nation's most popular pain relievers.

Acetaminophen – the active ingredient in Tylenol – is considered safe when taken at recommended doses. Tens of millions of people use it weekly with no ill effect. But in larger amounts, especially in combination with alcohol, the drug can damage or even destroy the liver.

Davy Baumle, a slender 12-year-old who loved to ride his dirt bike through the woods of southern Illinois, died from acetaminophen poisoning. So did tiny five-month-old Brianna Hutto. So did Marcus Trunk, a strapping 23-year-old construction worker from Philadelphia.

The toll does not have to be so high.

The U.S. Food and Drug Administration has long been aware of studies showing

Major Takeaways

1 About 150 Americans die a year by accidentally taking too much acetaminophen, the active ingredient in Tylenol, federal data from the CDC shows.

2 Acetaminophen has a narrow safety margin: the dose that helps is close to the dose that can cause serious harm, according to the FDA.

3 The FDA has long been aware of studies showing the risks of acetaminophen. So has the maker of Tylenol, McNeil Consumer Healthcare, a division of Johnson & Johnson.

the risks of acetaminophen – in particular, that the margin between the amount that helps and the amount that can cause serious harm is smaller than for other pain relievers. So, too, has McNeil Consumer Healthcare, the unit of Johnson & Johnson that has built Tylenol into a billion-dollar brand and the leader in acetaminophen sales.

4 Over more than 30 years, the FDA has delayed or failed to adopt measures designed to reduce deaths and injuries from acetaminophen. The agency began a comprehensive review to set safety rules for acetaminophen in the 1970s, but still has not finished.

5 McNeil, the maker of Tylenol, has taken steps to protect consumers. But over more than three decades, the company has repeatedly opposed safety warnings, dosage restrictions and other measures meant to safeguard users of the drug.

Yet federal regulators have delayed or failed to adopt measures designed to reduce deaths and injuries from acetaminophen overdose, which the agency calls a "persistent, important public health problem."

The FDA has repeatedly deferred decisions on consumer protections even when they were endorsed by the agency's own advisory committees, records show.

In 1977, an expert panel convened by the FDA issued urgently worded advice, saying it was "obligatory" to put a warning on the drug's label that it could cause "severe liver damage." After much debate, the FDA added the warning 32 years later. The panel's recommendation was part of a broader review to set safety rules for acetaminophen, which is still not finished.

Four years ago, another FDA panel backed a sweeping new set of proposals to bolster the safety of over-the-counter acetaminophen. The agency hasn't implemented them. Just last month, the FDA blew through another deadline.

Regulators in other developed countries, from Great Britain to Switzerland to New Zealand, have limited how much acetaminophen consumers can buy at one time or required it to be sold only by pharmacies. The FDA has placed no such limits on the drug in the U.S. Instead, it has continued to debate basic safety questions, such as what the maximum recommended daily dose should be.

For its part, McNeil has taken steps to protect consumers, most notably by helping to fund the development of an antidote to acetaminophen poisoning that has saved many lives.

But over more than three decades, the company repeatedly fought against safety warnings, dosage restrictions and other measures meant to safeguard users of the drug, according to company memos, court records, documents obtained under the Freedom of Information Act, and interviews with hundreds of regulatory, corporate and medical officials.

Safety Delay

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38	9	7	16	57	47
YEARS	MONTHS	DAYS	HOURS	MINUTES	SECONDS

In the 1970s, the Food and Drug Administration appointed an expert panel to review the safety and efficacy of over-the-counter pain relievers, including acetaminophen, the active ingredient in Tylenol. The panel delivered their recommendations on April 5, 1977. At the time, the FDA estimated it would issue final regulations before the end of 1978. The agency has still not completed its work. This is how much time has passed since then. Find out more »

In the 1990s, McNeil tried to create a safer version of acetaminophen, an effort dubbed Project Protect. But after the initiative failed, the company kept its

experiments confidential , even when the FDA inquired about the feasibility of developing such a drug.

Later, McNeil opposed even a modest government campaign to educate the public about acetaminophen's risks, in part because it would harm Tylenol sales.

All the while, it has marketed Tylenol's safety. Tylenol was the pain reliever "hospitals use most," one iconic ad said. The one "recommended by pediatricians," said another. "Safe, fast pain relief," its packages promised.

In written responses to questions for this story, as well as
▶ a pre-recorded statement by its vice president for medical affairs, McNeil said it has always acted to ensure its products were used safely.

"McNeil takes acetaminophen overdose very seriously, which is why we have taken significant steps over the years to mitigate the risk," the company wrote. McNeil has engineered safety packaging and spent millions on research, education and poison control centers that advise people who have overdosed .

The company said that science on acetaminophen had evolved over time and that it had implemented safety measures accordingly . Most recently, it announced it will soon add red lettering to the caps of medicine bottles saying they contain acetaminophen and that users should read the label.

In several cases, after FDA advisors recommended the agency enact safety measures over McNeil's objections, the company adopted them before the agency forced it to do so. The company then said it was taking such steps voluntarily. McNeil also stressed that it has always followed FDA regulations.

McNeil objected to the thrust of questions from ProPublica and This American Life, saying they indicated "a clear bias" in favor of plaintiff's lawyers who are suing the company.

The company declined to answer questions about individual cases of death or injury. "Our hearts go out to those who have suffered harm from acetaminophen overdose, and to the families of those who lost their lives as a result," McNeil wrote in its statement.

FDA officials said the agency saw the benefits of keeping acetaminophen widely available as outweighing the "relatively rare" risk of liver damage or death. Some patients cannot tolerate drugs such as ibuprofen, and for them acetaminophen may be the best option, said one agency official.

Accidental Deaths by Acetaminophen Poisoning

How many people have died by accidentally overdosing on acetaminophen each year.

1,567

Number of people who have died from 2001 through 2010 from inadvertently taking too much acetaminophen.

Source: U.S. Centers for Disease Control and Prevention Multiple Cause of Death database

The FDA has bolstered acetaminophen warnings as new science about the drug emerged, the agency said in a statement.

Brianna's Story:

"She Didn't Have a Second Christmas"

Read the story »

But FDA officials acknowledged the agency had moved sluggishly to address the mounting toll of liver damage caused by acetaminophen. They blamed changing research, small budgets, an overworked staff and a cumbersome process for changing rules for older drugs such as Tylenol slowing them down.

The agency has greater authority over prescription drugs, and it has already slapped medications containing acetaminophen with a “black box warning” that says overdosing can lead to “ liver transplant and death .” Paradoxically, the same medicine sold over the counter does not tell patients that death is a possible side effect.

“Among over-the-counter medicines, it’s among our top priorities,” said Dr. Sandy Kweder, one of the FDA’s top experts on acetaminophen. “It just takes time.”

Many doctors believe in acetaminophen and some medical associations advise patients to take it for mild to moderate pain or reducing fever. “Given the number of doses given annually, the track record is incredibly safe,” said Dr. Bill Banner, a pediatrician and the medical director of the Oklahoma Poison Control Center.

Every over-the-counter pain reliever can cause harm. Even without overdosing, aspirin and ibuprofen can lead to stomach bleeding. In extremely rare cases, according to the FDA, recommended doses of ibuprofen and acetaminophen can provoke a skin reaction that can kill.

But the FDA says acetaminophen carries a special risk. About a quarter of Americans routinely take more over-the-counter pain relief pills of all kinds than they are supposed to, surveys show. That behavior is " particularly troublesome " for acetaminophen, an FDA report said, because the drug's narrow safety margin places " a large fraction of users close to a toxic dose in the ordinary course of use .”

The FDA sets the maximum recommended daily dose of acetaminophen at 4 grams, or eight extra strength acetaminophen tablets. That maximum applies to both over-the-counter and prescription drugs with acetaminophen.

Taken over several days, as little as 25 percent above the maximum daily dose – or

just two additional extra strength pills a day – has been reported to cause liver damage , according to the agency. Taken all at once, a little less than four times the maximum daily dose can cause death. A comparable figure doesn't exist for ibuprofen, because so few people have died from overdosing on that drug.

About as many Americans take ibuprofen as take acetaminophen, according to consumer surveys from the mid-2000s .

The U.S. Centers for Disease Control and Prevention and the American Association of Poison Control Centers collect data on the number of deaths associated with each drug, but the figures are incomplete, making comparisons subject to question. McNeil contends the databases do not contain the information needed to draw conclusions about the relative risks of different medicines. The company and some epidemiologists maintain that these data sets undercount deaths resulting from chronic use of naproxen, ibuprofen and similar pain relievers. (More on the numbers can be found here.)

Still, the data show that acetaminophen is linked to more deaths than any other over-the-counter pain reliever.

From 2001 to 2010, annual acetaminophen-related deaths amounted to about twice the number attributed to all other over-the-counter pain relievers combined, according to the poison control data.

In 2010, only 15 deaths were reported for the entire class of pain relievers, both prescription and over-the-counter, that includes ibuprofen, data from the CDC shows.

That same year, 321 people died from acetaminophen toxicity, according to CDC data. More than half – 166 – died from accidental overdoses. The rest overdosed deliberately or their intent was unclear. For the decade 2001 through 2010, the data shows, 1,567 people died from inadvertently taking too much of the drug.

Acetaminophen overdose sends as many as 78,000 Americans to the emergency room annually and results in 33,000 hospitalizations a year, federal data shows. Acetaminophen is also the nation’s leading cause of acute liver failure, according to data from an ongoing study funded by the National Institutes for Health.

Behind these statistics are families upended and traumatized and, in the worst cases, shattered by loss.

Udosha Baumle sits by the gravestone of her son Davy, who died at age 12 of liver failure after taking Maximum Strength Tylenol Sore Throat. (Melanie Burford for ProPublica)

Just before Christmas 1999, 12-year-old Davy Baumle came down with a sore throat. For a week, his parents, David and Udosha Baumle, gave him Maximum Strength Tylenol Sore Throat, measuring out doses of the thick syrup.

But instead of getting better, Davy became listless. On Christmas Day, he threw up blood. His father took him to a local emergency room wrapped in a fuzzy brown blanket. A few days later, the boy was declared brain dead.

The Baumles later sued McNeil, claiming the company had failed to warn consumers of its product's lethal danger. At trial, they testified they never gave Davy more than the recommended dose, 4 grams per day, or eight tablespoons. An expert for the company testified that lab work suggested the boy had ingested more, 6 to 10 grams, over several days .

The difference amounted to as little as 4 tablespoons a day, but the company prevailed, persuading the jury that the Baumles had not used Tylenol precisely as specified.

David Baumle said he would never have given his son the drug if he knew it was potentially lethal. At the time, the label simply warned of "serious health consequences" in case of overdose.

"They tell you it's medicine," he said. "They don't tell you it can kill you."

"They tell you it's medicine... They don't tell you it can kill you."

David Baumle, father of Davy Baumle

Tylenol was born in 1955, when the family-owned McNeil Laboratories introduced a liquid for children called Tylenol Elixir.

The drug's key ingredient, acetaminophen, was developed in the late 1800s in Germany's coal tar industry. McNeil seized on the drug's potential after American research suggested that the medication does not cause stomach bleeding, as aspirin can. McNeil

named the product based on letters in the chemical term for acetaminophen, N-ace**tyl**-p-aminoph**enol**.

McNeil Consumer Healthcare, maker of Tylenol. Insiders call it The Fort. (J. Kyle Keener for ProPublica)

Johnson & Johnson acquired McNeil in 1959, the same year that Tylenol was approved for over-the-counter sales. Soon thereafter, the first adult version of Tylenol rolled off the company's production line in Fort Washington, Pa., the site of McNeil's current headquarters.

Unlike companies that develop prescription drugs, McNeil has no patent on acetaminophen, and so no right to sell it exclusively. Virtually every drug store stocks generic acetaminophen, usually on the same shelf as Tylenol. To sell Tylenol at a premium, the company had to persuade customers they were getting extra value.

Tylenol has had "generic competition for 40 years," said Ashley McEvoy, then the president of McNeil, in a webcast interview posted in 2008. "If I look back at what's garnered success for McNeil, it's the enduring value of brands."

The company aimed its early sales pitches at doctors, according to a company history, working to persuade them to recommend Tylenol as a safer alternative to aspirin. To this day, the company's formula for success hinges on positioning Tylenol as safer than other painkillers and more trustworthy than generics.

Perhaps the most famous chapter in McNeil's corporate history is its response when several people in the Chicago area died in 1982 after taking Tylenol laced with cyanide.

The mysterious deaths terrorized the country — and raised questions about the safety of the company's products. But in what later became a business school case study, McNeil removed Tylenol from the market, offered refunds and eventually developed tamper-resistant pills. By the end, it had transformed a disaster into a public relations coup.

"If I look back at what's garnered success for McNeil, it's the enduring value of brands."

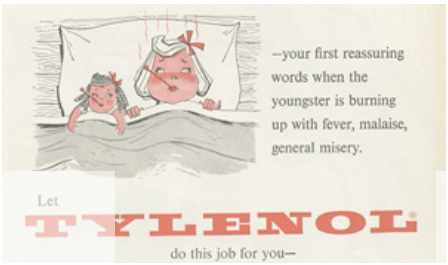
Ashley McEvoy, former president of McNeil, the Johnson & Johnson unit that makes Tylenol

McNeil's marketing campaigns for its master brand were also skillful, burnishing Tylenol's image while usually avoiding claims of absolute safety or zero side effects. One slogan: "The brand of pain reliever that doctors recommend more than any other." Another: "Trust TYLENOL. Hospitals do."

"We never use the word 'safe' in our advertising," said Anthony Temple, McNeil's longtime medical director, in a legal case in 1993. "We will say 'a superior safety profile' or some language to suggest its relative safety to other" over-the-counter pain relievers.

A History of Advertising

Marketing prowess helped turn Tylenol into one of America's most popular pain relievers. Over the past decade, McNeil Consumer Healthcare, the unit of Johnson & Johnson that makes Tylenol, has often spent more than $100 million per year on advertising the drug, according to advertising trade publications. See ads and commercials from some of the company's campaigns.



McNeil's advertising budget for Tylenol has frequently exceeded $100 million per year: $115 million in 2003, according to Brandweek; $138 million in 2005, according to Advertising Age; and $162 million in 2008, according to Adweek. In 2004, marketing was the largest department in the company, employing about 150 professionals, McEvoy said in a court deposition.

McNeil's recent chief executives have often come from marketing backgrounds. Johnson & Johnson, a conglomerate of more than 250 companies, does not even place McNeil into its pharmaceutical division, which is responsible for prescription drug products. Instead, the company is part of the consumer division, along with shampoo, mouthwash and skin care products.

Johnson & Johnson does not release sales figures for individual products, but Tylenol is the dominant acetaminophen brand in the U.S. Although the drug is available in cheaper generic forms, McNeil accounted for nearly half of all over-the-counter sales of acetaminophen, according to a 2010 McNeil presentation .

Sales of acetaminophen by all companies have also grown. It became the nation's most-used drug in the mid-2000s, according to surveys. In 2009, more than 27 billion doses of acetaminophen were sold in the U.S., most over the counter.

One way McNeil has reached ever-more households is through a marketing strategy known as line extension: targeting market niches by adding products, all under the halo of the Tylenol brand. Between 1988 and 2002, the company notified the FDA of plans to introduce 54 different kinds of packages, ranging from chewable tablets to coated pills, packed into bottles, pouches, cartons and blister packs.

In the webcast interview, McEvoy, a marketing expert who rose into Johnson & Johnson's corporate ranks, called Tylenol "a billion-dollar brand."

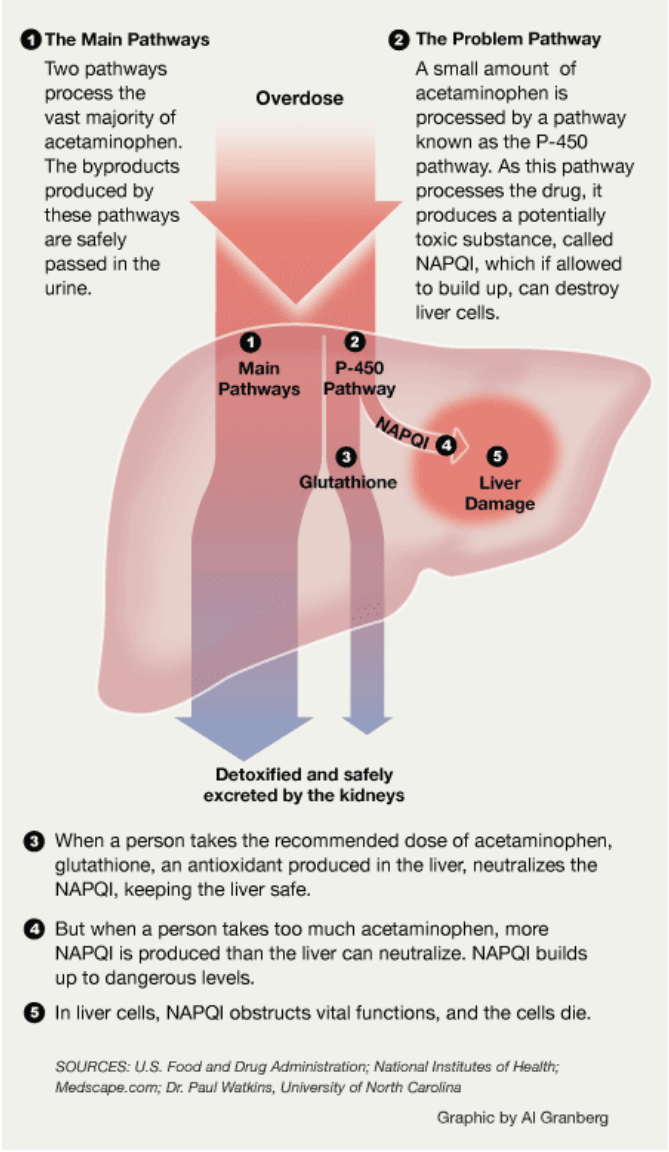
Internally, company officials refer to it simply as "the Brand."

The first reports of deaths from acetaminophen emerged in the late 1960s.

How the Liver Processes Acetaminophen

The liver uses multiple enzyme systems, known as pathways, to

process acetaminophen and remove potentially toxic byproducts produced during metabolism. In the case of an overdose, these pathways become overwhelmed, allowing the byproducts to build up to toxic levels, resulting in damage to the liver.



Researchers subsequently learned that when the drug is broken down in the liver, it produces a potentially toxic byproduct. In an overdose, the liver can no longer safely dispose of the byproduct and can fail in a matter of days, shriveling like a deflated balloon.

The concerns with acetaminophen emerged at a time when the American system for drug oversight was undergoing a sea change. Congress had passed a law in 1962 requiring the FDA to institute more rigorous testing for new drugs and to review the safety and efficacy of those already on the market.

In 1972, as part of the review of existing drugs, the FDA assembled a group of doctors and scientists to assess painkillers, including acetaminophen.

Over five years, the panel held 50 meetings, heard from scores of witnesses, and scoured thousands of pages of research – much of it submitted by drug makers themselves.

As the panel's work was going on, one of the world's most prestigious medical journals weighed in on acetaminophen. The London-based Lancet declared in a 1975 editorial that if the drug "were discovered today it would not be approved" by British regulators. "It would certainly never be freely available without prescription."

The journal's editorial board called the drug's apparent safety "deceptive." They pointed out that "not much more than the recommended maximum daily dosage" could cause liver damage and that acetaminophen poisoning was already "one of the commonest causes" of liver failure in Britain. (The drug is known there and in many countries as paracetamol.)

Relatively few cases of acetaminophen poisoning had been documented in the United States. But an American study published in 1975 identified four acetaminophen-related deaths in one year in one city, Denver. The article suggested a reason why so few cases had previously been found: "If you do not look for something you will not diagnose it."

McNeil dispatched a top official to meet with one of the study's authors. The company then gave him funding to help develop the acetaminophen antidote.

Two years later, in 1977, the FDA's expert panel delivered its 1,200-page report on pain relievers.

While the committee found that acetaminophen was generally safe when used as directed, it warned that "some advertising for acetaminophen gives the impression that it is much safer than aspirin." So the panelists urged the FDA to add a clear, specific warning to the acetaminophen label.

The language the panel suggested: "Do not exceed recommended dosage because severe liver damage may occur." The panel had only advisory power, but it felt so strongly that it told the FDA the warning was "obligatory."

Committee members wanted to drive home the potentially devastating consequences of taking too much acetaminophen, said Ninfa Redmond, a toxicologist who served on the panel.

"We felt very strongly the evidence was conclusive," Redmond said.

For McNeil, the proposed liver warning put a lot at stake. Just the year before, Tylenol had become the No. 1 brand in the over-the-counter pain medication market, according to a company history.

As McNeil prepared its response to the advisory panel's recommendation, new reports of harm from the drug emerged.

In September 1977, the Annals of Internal Medicine published articles about patients who suffered liver damage after taking acetaminophen for an extended period of time at or slightly above therapeutic doses, underscoring what the Lancet had said about the drug's narrow margin for error.

> If acetaminophen "were discovered today it would not be approved" by British regulators.
>
> **1975 editorial in The Lancet, a London-based medical journal**

That December, McNeil filed a voluminous response to the FDA opposing the recommendation for a liver warning. It's not known if the individuals who drafted the company's filing were aware of the journal articles, but the company asserted that people who overdosed were "almost invariably" trying to kill themselves. Indeed, McNeil maintained it had never seen a "documented case" of a person harmed while taking the drug for medical reasons.

A liver warning "is unnecessary and serves only to confuse and frighten the vast majority of consumers who use acetaminophen in a rational and appropriate fashion," the company concluded. It also wouldn't help consumers, the company said, because signs of liver damage often don't emerge until it's too late to get help.

McNeil raised another objection: The warning would put it at a competitive disadvantage.

What Do You Think?

Should American drugmakers | Should the FDA require all | Who's most to blame for deaths

have to limit acetaminophen pills sold over-the-counter?

WEIGH IN

acetaminophen drugs to carry black box warnings?

WEIGH IN

caused by mixing up Tylenol products for infants and children?

WEIGH IN

Bayer, one of the world's largest aspirin makers, had started running advertisements citing acetaminophen's potential to harm the liver, based on the advisory panel's recommendation. "Losses are already in the millions of dollars," McNeil stated in its submission to the FDA.

Almost a decade would pass without the FDA coming to any decision. While the label advised consumers to seek medical assistance if they overdosed, McNeil was able to sell its drug without warning that it could harm the liver. The agency's decision was delayed, at least in part, because regulators extended deadlines to review new research.

Redmond called such additional review unnecessary because the basic facts about the drug were well-established. She said she was mystified by regulators' failure to act on the panel's recommendation. "It's very surprising, and it's sad," she said. "How many people might have died because of that?"

Finally, in 1988, the FDA announced a "tentative" ruling. The agency agreed a warning was necessary but said there was no need to specify that the drug could injure the liver.

The agency explained that it didn't want people who were considering suicide to know what an overdose could do. And, it said, liver damage didn't produce telltale symptoms for several days, when it was often too late for doctors to intervene.

So it mandated a catchall warning: In case of overdose, consumers should seek prompt medical attention "even if you do not notice any signs or symptoms."

McNeil had won a reprieve from having to put a phrase on its bottles that company officials believed scared off buyers: "severe liver damage." And the FDA would not return to the issue until many, many years later.

How Much Acetaminophen Are You Taking?

Use this tool to find out which of the drugs in your medicine cabinet contains acetaminophen -- and how much. Note: A single dose may be more than the amount shown. For example, one pill might contain 325 mg but the recommended dose might be two pills, or 650 mg. Source: National Library of Medicine

Tylenol Search

650 mg Acetaminophen in 1 tablet	650 mg Acetaminophen in 1 tablet	500 mg Acetaminophen in 1 tablet	500 mg Acetaminophen in 1 tablet	500 mg Acetaminophen in 1 tablet
Tylenol Arthritis Pain	Tylenol Arthritis Pain	TYLENOL Extra Strength	TYLENOL EXTRA STRENGTH	TYLENOL Extra Strength

Pain	Pain	Strength	STRENGTH	Strength
McNeil Consumer Healthcare Div McNeil-PPC, Inc	McNeil Consumer Healthcare Div McNeil-PPC, Inc	Cardinal Health	Lil' Drug Store Products, Inc.	McNeil Consumer Healthcare Div. McNeil-PPC, Inc
ENLARGE LABEL	ENLARGE LABEL	ENLARGE LABEL	ENLARGE LABEL	ENLARGE LABEL

As the FDA's deliberations over the label crawled on, research began to emerge about the risks of drinking alcohol and taking acetaminophen — and McNeil took steps to counter the research.

As early as the 1970s, an FDA panel had examined whether to put an alcohol warning on the acetaminophen label. In 1978, according to an internal McNeil memo, the company had been " successful in convincing " FDA officials "that such a warning was not indicated." But the issue had not gone away.

According to a corporate memo from February 1986 , McNeil had test-marketed how consumers would interpret different versions of an alcohol warning. No matter how the warning was phrased, consumers reacted negatively: Most respondents concluded that drinkers should reduce or discontinue using Tylenol, even at recommended levels.

The following month, the Annals of Internal Medicine published a study describing alcoholics who developed liver damage after taking "apparently moderate" amounts of acetaminophen.

Two weeks after the article's publication, a McNeil official issued a memo to Tylenol's sales force warning representatives to " not initiate discussions with your physicians " about the danger of mixing alcohol and acetaminophen. A senior McNeil official would later testify in a deposition that the issue was controversial and complex. Sales reps, he said, were "not equipped" to discuss it.

Then, in August 1987, a relatively obscure Swedish journal published a study on the dangers of drinking and taking acetaminophen.

Thomas Gates, then McNeil's medical director, shot off a memo to the chief executive of Johnson & Johnson , the president of McNeil and other top officials, laying out a detailed "plan of action" for "diffusing media interest" in the research and "limiting the extent and duration of the coverage."

Gates envisioned two possibilities : "Low Level of Publicity (most probable scenario)" and "High Level of Publicity (worst case scenario)." For the latter, Gates suggested a series of responses: a letter-writing campaign to medical societies, doctors, pharmacists and academics; a coordinated public relations response with the FDA; even placing on retainer scientists whose research the company favored.

"If there is another wave of publicity," Gates warned, "the FDA might be compelled to reconsider the matter and require a specific warning regarding a possible risk of toxicity in chronic alcohol abusers."

Gates, long retired from McNeil, was too ill to respond to questions, his wife said.

Ultimately, the Swedish study received little attention.

Gates' memo summarized cases in the scientific literature over the previous decade that documented acetaminophen's risk for drinkers. He wrote that 38 "chronic alcoholics" had reportedly suffered liver and/or kidney damage while taking acetaminophen. In just over half the cases, users substantially exceeded dosing limits.

However, there were 18 instances in which they took less than 6 grams a day, not much more than the 4 grams considered safe, Gates noted.

He stressed that "the amount of acetaminophen ingested is open to question since alcoholics are notoriously unreliable informants."

But "if accurate," he wrote, the amount of acetaminophen that harmed those 18 patients "bring us uncomfortably close" to the maximum recommended daily dose.

Although McNeil had been preparing for the possibility that the FDA would require an alcohol warning, it took years before the agency publicly grappled with the issue.

In 1993, the FDA convened an advisory panel to look at the risk of mixing alcohol and acetaminophen. Such panels are made up of outside experts. While the FDA does not have to follow their recommendations, it usually does.

McNeil argued against the warning, saying the scientific evidence did not justify it and that it would frighten customers into taking other pain relievers that the company claimed were riskier.

But the panel found that an alcohol warning was warranted. The chairman called the science behind it "unusually strong and well-supported."

At the same time, McNeil was seeking FDA approval for a new product, extended release Tylenol. Because it was a post-1962 drug, the agency could push for a warning with less red tape. It moved to do so on the new product, raising the possibility that regular Tylenol would have no alcohol warning but that the time-release product would have one.

After the FDA approved extended release Tylenol with an alcohol alert in 1994, McNeil voluntarily added the warning to all Tylenol products.

"After careful deliberation and discussion with the FDA, McNeil has made several label changes to Tylenol over the years — all for the purpose of eliminating potential confusion by consumers and protecting consumer safety," the company wrote in response to questions. "A label change does not mean that a prior label was inadequate, and in fact label changes are an indication that our medical understanding is evolving."

Four years after McNeil acted, the FDA required all acetaminophen manufacturers to add an alcohol alert to their products. People who drank three or more alcoholic drinks every day were advised to consult their doctors and were warned that liver damage could occur.

The warning label came too late for Antonio Benedi.

Benedi, who worked as a special assistant to President George H.W. Bush, often drank two or three glasses of wine with dinner. On a Friday in February 1993, just weeks after Bush left office, Benedi came down with the flu. Over the next several days, he said, he took Tylenol, never exceeding the maximum dose.

Benedi said he was careful to read labels. At the time, nothing on his box of Extra Strength Tylenol warned about the risk of drinking or liver damage.

Several nights later, he woke up, confused and incoherent. His wife called an ambulance to rush him to a hospital near their home in the Virginia suburbs of Washington, D.C.

By the time he arrived, Benedi had slipped into a coma. Tests showed his liver enzyme levels were high, a sign of organ damage. He had brain swelling, so doctors drilled a hole in his skull to relieve the pressure.

"When a company omits a known danger to them that could hurt people, they're lying to us. I think that is outrageous."

Antonio Benedi, who had a liver transplant after taking Tylenol, on McNeil, the Johnson & Johnson division that makes the drug

Antonio Benedi was forced to undergo an emergency liver transplant after just a few days of taking Tylenol. He won an $8.5 million verdict against McNeil, the Johnson & Johnson division that makes the drug. (Torsten Kjellstrand for ProPublica)

After his third day in a coma, Benedi got a second chance at life. Doctors declared a young man taken to Benedi's hospital after a motorcycle accident to be brain dead, and Benedi received the man's liver.

Benedi spent two months in the hospital, more than 200 surgical staples holding his abdomen together in a raw wound that looked like the Mercedes-Benz symbol.

Almost two decades later, he still suffers from those few days of taking Tylenol. To keep his body from rejecting his transplanted liver, he had to take powerful medications that eventually destroyed his kidneys, requiring a kidney transplant.

He sued McNeil. In court, the company argued that a virus had destroyed his liver and that the warnings on Tylenol's label were adequate. The jury found for Benedi, awarding him an $8.5 million judgment in 1994. To this day, he will have nothing to do with Tylenol — he always tells doctors and nurses not to give him any.

"I have nothing against corporations. They do a lot of good, employ a lot of people," said Benedi. But "when a company omits a known danger to them that could hurt people, they're lying to us. I think that is outrageous."

As Benedi's case unfolded, McNeil was pressing ahead with a program dubbed Project Protect to create a safer version of acetaminophen.

But the company kept the program, which has never been reported, confidential. Even when the government specifically asked for scientific information on developing a safer acetaminophen, the company didn't mention its own research.

The concept of such a drug was not new. The 1975 Lancet editorial had called for the development of a version of acetaminophen that wouldn't harm the liver . In the United Kingdom, companies had developed drugs combining acetaminophen with one of its antidotes. But sales never took off — the drugs were too expensive, the pills were too large, and there were questions about the drugs' safety.

"McNeil takes acetaminophen overdose very seriously, which is why we have taken significant steps over the years to mitigate the risk."

Statement by McNeil Consumer Healthcare, the maker of Tylenol

In the early 1990s, McNeil embarked on a series of experiments to combine acetaminophen with various protective agents . The effort involved almost 20 different lab and animal studies lasting several years, according to internal company documents and court records.

As the experiments progressed, however, one official worried that the research could be a double-edged sword.

A Johnson & Johnson manager based in Europe wrote to Ralph Levi, the head of Project Protect for McNeil, according to court documents. In his June 1994 note, the

Project Protect for McNeil, according to court documents. In his June 1994 note, the manager cautioned that a new, improved product touched on “a sensitive point,” because the company would be acknowledging that its existing product “isn’t so safe as we’ve always said before.” Levi has since died, and the court documents identified the manager only by his first name, Geert.

To help keep Project Protect hidden, the company signed a confidentiality agreement with Rutgers University, where some of the research was conducted. A key clause: The publicly funded university agreed not to publicize “the identity or interest of McNeil in this area of technology.” Rutgers said such agreements were standard when researchers worked with companies.

At least one line of research showed early promise, according to Rutgers documents, but there’s no public evidence that it or any Project Protect compound made it beyond laboratory or animal studies.

McNeil’s work remained confidential even after the FDA became interested in that field of research. In 2006, as part of a larger review of acetaminophen, the agency solicited information about combining the drug with antidotes.

In response, McNeil submitted a lengthy report citing 51 studies to document the drawbacks of such combinations. But the company did not mention that it had extensively researched the topic .

FDA officials said McNeil wasn’t required to disclose its research in that response. Asked if the company had ever told the agency of its project, the FDA did not answer. “Those are the kind of things that we are always interested in knowing about,” said Kweder, the FDA’s acetaminophen expert. She added that even “if they didn’t show anything, it’d be useful to us to know if didn’t work scientifically.”

In response to questions about Project Protect, McNeil acknowledged "research into acetaminophen overdose antidotes" but did not provide details. The company noted that confidentiality clauses are standard industry practice. It also said that the firm had complied fully with FDA reporting requirements.

The company said it halted the research after discovering that the most promising agent “posed a cardiovascular risk for individuals with a particular genetic defect.” The company did not disclose the name of the agent.

“Had the research yielded a viable discovery, our intention was to launch a product,” the company statement said. It continued: “Despite the outcome, we consider this type of research a responsible action on our part, and are proud of the many scientists who worked on it.”

As McNeil quietly pursued a safer acetaminophen, a bespectacled, bow-tied Dallas doctor named Will Lee was pursuing research that would change the debate about the drug.

“It’s just like candy. If four is good, eight must be better.”

In 1997, Lee published a groundbreaking paper in the New England Journal of Medicine showing that acetaminophen was the leading cause of acute liver failure at Parkland Memorial hospital in Dallas, despite the drug's "apparent overall safety."

Not to be confused with chronic liver failure, such as that caused by alcoholism, acute liver failure is a sudden, often fatal condition that affects about 2,000 Americans each year.

Among 21 patients who had overdosed on acetaminophen accidentally, Lee found, three reported that they had not exceeded the maximum recommended dose of 4 grams per day. Only seven said they had taken more than 10 grams.

Following the article, the National Institutes of Health funded a larger study involving many of the country's busiest liver transplant centers. Over the next 15 years, Lee, who is currently a professor of internal medicine at the University of Texas Southwestern Medical Center, confirmed that what he had documented in Dallas was true nationwide: Acetaminophen was the No. 1 cause of acute liver failure .

Over the years, almost half of the people in the study had overdosed by accident, Lee found, not by trying to kill themselves. Many of those patients had other risk factors; about one-fifth drank alcohol frequently.

One finding was downright counterintuitive : People trying to kill themselves with massive, one-time overdoses were more likely to survive than those who accidentally took too much.

The reason? The chemical antidote to acetaminophen poisoning that McNeil helped to develop has a high success rate if administered within eight hours of an overdose. Those who attempted suicide and later regretted their action often made it to a hospital in time.

Those who overdosed by accident were often unaware they had been poisoned. Their symptoms took several days to develop and resembled those of the flu, for which many of them had taken the drug in the first place. They were more likely to miss the window for the antidote.

Acetaminophen has "not been recognized as a poison — that's been part of the challenge," Lee said. "It's just like candy. If four is good, eight must be better."

McNeil disputed Lee's findings, saying they had "serious methodological weaknesses," such as relying upon patients

be better.

Dr. Will Lee, a professor of internal medicine at the University of Texas Southwestern Medical Center whose research has shown that acetaminophen is the leading cause of acute liver failure in the U.S., on the drug

to recall the amount of acetaminophen consumed.

But other researchers came to similar findings. At the Hospital of the University of Pennsylvania, Dr. Sarah Erush and a colleague found that half of 46 patients treated for acetaminophen-related liver damage over four years had overdosed accidentally, not intentionally.

The amount of acetaminophen these patients had ingested was close to the recommended daily dose of 4 grams. The median was 6 grams per day — a surprise, because the toxic dose was thought to be between 10 and 15 grams, Erush said. She also found that most of these patients had other risk factors, such as chronic alcohol use.

Although she didn't publish her research in a peer-reviewed journal, she ▶ presented it to the FDA .

"For almost every patient with accidental exposure, we said, 'Why did you take more than the recommended dose?'" Erush said in an interview. "They said two things: One, the label wasn't clear, and, two, they always thought it was a perfectly safe drug."

McNeil said that it had asked Lee and Erush for patient information in order to examine their conclusions. Both researchers said they had not provided McNeil such records, citing patient privacy issues.

Lee's research spurred the FDA to re-examine if the label on over-the-counter acetaminophen should explicitly warn about the risk of liver damage.

The agency invited a grieving mother to ▶ tell her story at a public hearing .

Kate Trunk's 23-year-old son Marcus had hurt his wrist in 1995 while working on a construction job in Pennsylvania. Over the next two weeks, he took Tylenol with Codeine and Extra Strength Tylenol. He started to feel sick and started on Theraflu — apparently not realizing that it, too, contained acetaminophen.

Soon, Marcus felt bad enough to check himself into a hospital, where he lapsed into a coma. Eight days after Marcus entered the hospital, Kate and her husband decided to end life support.

"We stayed with him and held him and talked to him and kissed him and petted him," Trunk said. "He finally just went. It was total shock, walking around in a daze, not knowing, angry at God, angry at everything."

The mystified family did not find out the cause of Marcus' death until the autopsy came back: liver failure caused by acetaminophen. The Trunks sued McNeil and settled for an undisclosed amount. McNeil did not respond to questions about the case.

When the Trunks took their concerns to the FDA hearing, Kate was so nervous that her husband kept checking her blood pressure. But she delivered a call to action: She wanted acetaminophen clearly labeled to warn that the drug could poison and even kill.

"If our son or my husband and I even had an inkling that acetaminophen toxicity existed, I feel that the outcome of our story would be totally different," she said. She ended her testimony by saying that "death is not an acceptable side effect."

"Death is not an acceptable side effect."

Kate Trunk, who lost her son to liver failure caused by acetaminophen, speaking before the FDA

The committee recommended adding a warning aimed at all users, not just drinkers, that overdosing can damage the liver.

This time, McNeil gave ground, agreeing with the need for a liver warning. "We believe with you that the American consumer is smart, responsible and can self-manage medications," Dr. Debra Bowen, McNeil's vice president of research and development, told the panel.

By 2005, McNeil began placing labels on Tylenol warning that taking too much could result in "liver damage" for anyone, not just people who drank alcohol.

In 2009, the FDA imposed stronger language, requiring all over-the-counter acetaminophen products to warn that overdosing may cause "severe liver damage."

The FDA's wording was nearly identical to what its expert panel had recommended 32 years earlier.

Asked about this time lag, the agency replied, "While we acknowledge that there has been some delay between available scientific information and the translation to labeling instructions for consumers, FDA has strengthened warnings on the acetaminophen label accordingly as science has evolved."

While McNeil agreed on the need to warn consumers of acetaminophen's potential to harm the liver, it vigorously objected to the FDA's plans to raise public awareness of that very risk.

In 2004, the agency launched a modest public service advertisement initiative. The slogan: "Why is it important to know that all these medicines contain acetaminophen? Because too much can damage your liver."

A key problem the campaign hoped to address: double dipping, or overdosing by inadvertently taking more than one medication that contains acetaminophen.

That risk had grown as McNeil and its competitors expanded the number of acetaminophen products on drugstore shelves. The drug was in medications targeted at consumers suffering all manner of ills, from colds to arthritis aches to insomnia

The FDA's 2004 public service

caused by pain.

The FDA's 2004 public service announcement. (FDA)

The FDA didn't have a lot of money for the 2004 campaign, just $20,000, according to an Associated Press story from the time.

During this period, McNeil was spending more than $100 million a year to advertise Tylenol, trade publications reported.

Nevertheless, McNeil launched an intense and lengthy effort to overhaul the campaign.

The company sent a 79-page complaint demanding that, if left unchanged, the FDA's educational campaign would " negatively affect McNeil, the world's largest marketer of OTC acetaminophen products ."

Indeed, the complaint said, the FDA should speed up its review "in order to limit the damage that is being done" by the nascent campaign.

McNeil wanted the FDA to include warnings about other over-the-counter pain relievers, arguing that they posed risks at least as serious as acetaminophen. The FDA's initiative, the company contended, created the false impression that "acetaminophen products are less safe" than other over-the-counter painkillers and could spur consumers to switch to other pain medicines, resulting in more injuries and deaths – a frequent McNeil argument .

The FDA's Steven Galson, then the acting director of the agency's Center for Drug Evaluation and Research, disagreed.

Doubling the maximum daily dose of over-the-counter pain killers such as aspirin or ibuprofen "may slightly increase a person's risk for bleeding," in the stomach and gastrointestinal tract, he wrote, but " it is not even close to the seriousness presented by doubling the dose of acetaminophen ," which can lead to liver failure.

McNeil took its case all the way to the FDA commissioner, who turned down the company's final appeal, saying the agency had "refuted each example to respond to your allegation ."

McNeil did not respond directly to questions about its opposition to the campaign.

But it stressed that it had launched numerous acetaminophen safety education efforts , both on its own and with industry and government partners. Altogether, McNeil said, these "acetaminophen awareness messages have been seen over one billion times ."

Although the agency had prevailed, its safety initiative fizzled. Major media outlets were reluctant to run the public health announcements. Magazine publishers told agency officials that they "did not want to antagonize potential advertisers,"

according to an FDA report .

The FDA concluded that its campaign "did not appear to have a significant impact on the problem."

Indeed, a nationwide poll this year shows that many Americans don't recognize the risk of double dipping.

Thirty-five percent of respondents said it was safe to take the maximum recommended dose of Extra Strength Tylenol with NyQuil, a cold remedy that also

recommended dose of Extra Strength Tylenol with NyQuil, a cold remedy that also contains acetaminophen. The margin of error was 3.5 percentage points.

Among parents, 35 percent thought it was safe to give a child the maximum dose of Children's Tylenol with Children's Tylenol Plus Multi-Symptom Cold, both of which contain acetaminophen. The margin of error for the parents' subgroup was 6.7 percentage points.

In both these examples, mixing the two medicines would not be safe, according to the FDA.

(The survey of 1,003 respondents – conducted by Princeton Survey Research Associates International and commissioned by ProPublica and This American Life – was completed in March.)

What's in a Dose?

You may be familiar with some of these over-the-counter and prescription drugs, and may have even taken more than one at the same time. Because so many drugs contain acetaminophen, people can inadvertently take more than the recommended daily limit – or even hit a dangerous dose. Click on a drug to see the maximum daily dose recommended on the label, and how quickly it adds up in combination with others. Click on the drug again to remove it from the acetaminophen tally. Please note: This is not meant to be medical advice. Toxic levels vary by individual. Call your doctor if you think you've overdosed, even if you don't show medical symptoms. Source: National Library of Medicine

Click on a drug to see its daily limit of acetaminophen

With the public education campaign faltering, the FDA regrouped in 2006 and convened a team to examine the agency's handling of acetaminophen — including what a former top official described as "the interactions between the FDA and McNeil over this 30-year history."

Officials reviewed the science, the reports of deaths and side effects, and the long history of regulatory delays. The 265-page report that emerged was both a blunt

assessment of the drug's dangers and a plan for mitigating them.

Officials concluded that deaths from acetaminophen poisoning had risen dramatically over the decade between 1995 and 2005. They zeroed in on how the drug differed from other over-the-counter pain relievers.

"The 4 gram per day recommended dose is also the maximum safe dose, one that must not be exceeded, an unusual situation for any drug, particularly an OTC drug, one placing a large fraction of users close to a toxic dose in the ordinary course of use," the report said.

Officials proposed more than a dozen solutions, including several aimed at widening the drug's safety margin, such as lowering the maximum recommended daily dose and reducing the amount of the drug in each pill. The report also suggested removing an entire class of pediatric products to reduce the potential for dosing mix-ups.

Taken together, the proposals constituted a blueprint for sweeping safety reforms.

At the same time, the FDA officials who wrote the report gave a candid assessment of the fierce resistance they expected from drug makers to certain proposals.

To the notion of lowering the recommended daily dose, the agency expected a "possible industry challenge."

To the proposal to decrease the amount of acetaminophen per pill, the report anticipated "possible industry resistance to costs related to reformulation" and to "possible loss of revenue from elimination of 500 mg products."

In June 2009, the agency gathered nearly 40 experts in a Maryland Marriott to weigh in on its recommendations. Everyone in the room, including executives from McNeil and other companies, knew the stakes.

Edwin Kuffner, McNeil's medical director, had prepared for the meeting by attending some 100 practice sessions with a consulting company that specialized in readying corporate clients to speak before the FDA, according to a court deposition.

Kuffner objected to dropping the daily recommended dose below 4 grams. For decades, the company's labels had advised users to take no more than 1 gram, or the equivalent of two Extra Strength Tylenol pills, at a time. He ▶ suggested directing consumers to take one pill at a time until they felt pain relief, gradually easing up to a maximum of 4 grams a day only as necessary. Even though a company document calls this practice " good medicine ," McNeil has not added this instruction to Tylenol labels.

When it came time to vote, Judith Kramer, a physician and professor of medicine at Duke University, reminded her fellow panelists of the opportunity before them, noting that attempts to make acetaminophen safer had foundered for decades.

"There is an elephant in the room that we really should talk about explicitly," she said. "There are tremendous cost and commercial implications to some of the

Guides to Safe Use

Here are some sites that offer information on how to safely use acetaminophen. ProPublica does not endorse any of these sites and is not offering medical advice. If you have a medical issue, contact a doctor.

National Institutes of Health

McNeil

Consumer Health Products Association and others

Mayo Clinic

Food and Drug Administration

said? "There are tremendous cost and commercial implications to some of the recommended changes. These conditions frequently can overshadow the public health considerations. And I think that we can't let that happen."

The panel handed McNeil a defeat, endorsing most of the FDA's proposals.

But then, the agency's momentum stalled.

Four years later, the agency has not enacted any of its own suggestions for over-the-counter acetaminophen.

In fact, the FDA has still not completed the review of the drug that began back in the 1970s, as part of the agency's larger mandate to assess the safety and efficacy of older medicines.

In interviews, FDA officials acknowledged that it has taken longer than it should. They blamed a combination of science and bureaucracy.

Despite 50 years of sales and more than 30,000 published papers, there remain unknowns about acetaminophen. In a little-publicized 2011 announcement, the FDA acknowledged it was still unable "to identify precise toxic thresholds and/or specific populations for whom currently recommended dosages are not safe."

A Canadian government study found six people had suffered serious liver damage after taking less than the maximum recommended dose. By contrast, a case report described a man who survived after ingesting as much as 60 grams all at once. In response to questions, McNeil first wrote in an email that 8 grams, or double the maximum daily dose, over several days can damage the liver. Later, when asked to confirm this figure, the company declined to do so. It pointed to data showing that at least 10 grams a day for at least 2 to 3 days can threaten the liver.

Setting the right dose "has been one of the big challenges for us," the FDA's Kweder said. "There is so much disagreement among experts who are well respected and can present data on where they'd draw that line."

Agency officials also said that McNeil has often resisted changes.

McNeil was "more aggressive than most," a former top FDA official said. "It's a company that feels very strongly about the competitive nature of the marketplace."

McNeil countered: "Our marketing practices are appropriate and align with the regulatory standards for our industry."

It also added that the company had a "deep respect for the Food and Drug Administration (FDA) and its role in establishing and enforcing regulations" and noted that it has voluntarily implemented some safety measures before the agency required it to do so.

The FDA delays are, at least in part, self-inflicted.

The agency said that the procedure it set back in the 1970s for revising rules for older drugs "was not rapid, but there were many fewer steps to the process that today is long." Indeed, actions that were supposed to take months have dragged on for years

or even decades.

For prescription drugs, the FDA can act more swiftly, and it has limited the amount of acetaminophen in such medicines.

In 2011, the FDA limited the amount of acetaminophen that can be put in prescription drugs to 325 milligrams per pill, and gave companies until January 2014 to implement the change.

Yet the agency continues to allow the sale of over-the-counter pills that contain up to 650 milligrams of acetaminophen — twice as much.

Asked why it permits such potent pills to be sold directly to consumers, an FDA official said the agency "believes there is a benefit to having acetaminophen available."

In addition to lowering the dose per pill, the FDA slapped prescription acetaminophen with a so-called black box warning, the agency's most serious. It states that "acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death."

The label for the over-the-counter version of the drug, taken by far more Americans, mentions neither of those potential consequences.

The agency's disparate actions on prescription and over-the-counter acetaminophen have given rise to glaring inconsistencies.

Tylenol with Codeine No. 3, made by a Johnson & Johnson company, combines acetaminophen with codeine, which can be bought only with a prescription. Tylenol 3, as it is commonly known, carries a black box warning about acetaminophen, and each pill contains 300 milligrams, less than the new limit of 325 milligrams.

By contrast, a single pill of Extra Strength Tylenol — sold at newsstands, gas stations and big-box retailers across the land — delivers 500 milligrams of acetaminophen. The bottle carries no black box warning.

Two pills, containing the same medication, made by the same corporation, carrying the same brand name, regulated by the same agency – but subject to different standards.

While the FDA remains stuck on rules for over-the-counter acetaminophen, McNeil has reversed course on one major proposal.

Just a month after adamantly opposing dosing reductions at the 2009 advisory committee meeting, McNeil wrote top FDA officials, offering a plan that recognized the will of the advisory committee .

Although the company had insisted for half a century that 4 grams of medicine per day was the most appropriate dose for pain relief, the company said it was ready to recommend taking no more than 3 grams a day (or six pills) of its flagship product, Extra Strength Tylenol. The company implemented the change in 2011.

The move echoed other instances, such as the alcohol warning, in which the company opposed safety proposals until the FDA signaled its intent. Then the company adopted measures voluntarily as the agency plodded toward final rules.

Kuffner, McNeil's vice president for medical affairs, said in an interview that the company changed its dosing instructions "after hearing the discussion" at the 2009 advisory committee. The lower dose is "intended to increase the margin of safety," he said.

"There are still many questions about this drug... It's still killing people."

Dr. Thomas Garvey, a former FDA official and drug industry consultant on acetaminophen. He has testified against McNeil, the manufacturer of Tylenol.

McNeil hasn't standardized the new daily dose across all its products, however. For Tylenol Arthritis Pain, the company's label puts the daily limit at 3.9 grams. And the company didn't change the dose for customers worldwide. In Canada and other countries, the company still instructs users of Extra Strength Tylenol that they can take up to 4 grams a day — eight pills.

Kuffner said the "root causes" of acetaminophen overdose differ from region to region.

"The safety of consumers in every region is important to us. When you really go back and look at root causes, some of the root causes weren't as prevalent as in other regions," he said. "There are differences in the prevalence of acetaminophen overdose and liver injury."

"At the end of the day, when people take 4 grams or 3 grams, both of them are safe doses," Kuffner said.

The FDA had said it would issue proposed rules for over-the-counter acetaminophen by the end of August. But the agency missed that deadline, pushing it back to December.

Dr. Thomas Garvey, a former FDA official and drug industry consultant who has testified against McNeil in trials, called the amount of time the FDA had taken to reach a final ruling "remarkable and unusual."

"There are still many questions about this drug," Garvey said. "It's still killing people."

In many other countries, authorities have taken a very different approach to regulating acetaminophen.

At least 10 other industrialized countries — including Australia, New Zealand, Germany, Finland, Denmark, Sweden and Switzerland — have placed some kind of restrictions on the drug, a 2008 FDA report said. Most limit how much can be sold at one time or

require pharmacies to be the only outlets that carry it.

Many countries restrict sales of acetaminophen, the active ingredient in Tylenol. Countries such as South Korea, the United Kingdom and Germany limit the amount of pills that can be sold in a package or where it can be sold. (Lars Klove for ProPublica)

Some European countries with strict regulations have remarkably few deaths. Switzerland's national toxicology center reported only four deaths due to acetaminophen poisoning from 1998 through 2012. Even accounting for Switzerland's much smaller population, that's a fraction of the U.S. toll.

The German government reported four deaths from acetaminophen poisoning in 2010, the same year the CDC put the American total at 321. The U.S. population is four times that of Germany.

Both Switzerland and Germany limit sales to pharmacies, which sell packages with a maximum of 10 grams, the equivalent of 20 Extra Strength Tylenol pills.

In many nations, authorities were focused more on reducing suicides than on preventing accidental overdoses. In the U.K., for example, acetaminophen had become a common suicide method by the 1990s. The drug was easy to get: In drug stores, it could be purchased in unlimited quantities.

In 1998, the U.K. cracked down on several types of pain relievers, including acetaminophen. At pharmacies, people could buy the equivalent of only 32 Extra Strength Tylenol pills. At other stores, they were limited to half that.

Here was a real-world experiment of the effect of restricting acetaminophen. Early studies were somewhat contradictory, but this year, a large study concluded that the number of deaths linked to acetaminophen had plunged by 43 percent. In the 11 years since the restrictions took effect, the researchers estimated, 765 fewer people had committed suicide using the drug.

While the new regulations may have saved lives, they hurt sales. The amount of acetaminophen sold in the U.K. plunged by 60 percent from 1998 to 2000, according to a study by the FDA. The agency noted that such restrictions would be more difficult to implement in the U.S. because it has a different commercial, regulatory and medical culture than Britain and many European countries.

Indeed, here there has been only limited debate about restricting the amount of acetaminophen consumers can buy.

A proposal to limit package sizes — how many pills could be put in a bottle, for example — was considered by the advisory panel convened by the FDA in 2009. In a close vote, it failed. Some of the experts worried that patients suffering from arthritis would be inconvenienced by having to make repeated trips to buy the drug.

Several committee members said they had struggled with their vote.

“I hope the FDA doesn't consider this ‘no’ vote to mean that we support selling 1,000 acetaminophen tablets in Costco,” said Kramer, the Duke University professor.

Over the past several years, McNeil and Tylenol have suffered a series of body blows related not to acetaminophen’s risks but to the company’s ability to manufacture its drugs safely. The headlines might have killed a lesser product, but have only underscored the extraordinary resiliency of the Brand.

Between 2008 and 2010, federal regulators discovered an array of troubling manufacturing violations at McNeil’s plants, triggering a series of recalls of Tylenol and other products such as the company’s Motrin brand of ibuprofen.

For example, to make Tylenol syrup for infants and children, the company used an ingredient that was possibly contaminated by dangerous bacteria. The company said “a thorough investigation” showed the bacteria had not reached its medicine. However, the FDA found that McNeil’s tests — skimming a teaspoon off the top of a container of liquid — were inadequate.

Later, agency investigators also discovered that Tylenol and other products had been contaminated by tiny bits of cadmium, nickel, chromium, iron and other metals, most likely shavings that fell into the medicine from machines on the production line.

Again, McNeil officials saw little cause for concern. “We are talking minute particles,” one McNeil employee told FDA officials. “We are talking contaminants you don’t want to be there!” an inspector replied, according to previously unreported notes taken by McNeil.

taken by McNeil.

The company itself determined that it had manufactured batches of what the FDA called "super potent" Infants' Tylenol with up to 23 percent more acetaminophen than was supposed to be in it. It is not known if any reached the market.

On April 30, 2010, the FDA issued a formal inspection report with a litany of deficiencies. The same day, McNeil pulled 136 million bottles of pediatric Tylenol and other medicines off the market.

It was the largest recall in the history of pediatric medicine.

Subsequently, the Department of Justice launched a civil investigation that effectively gave the FDA power to direct the cleanup of McNeil's troubled plant in Fort Washington, Pa. The FDA has not tied any recalled product to individual cases of harm.

Congress hauled in company executives for two public hearings. William C. Weldon, then chairman and chief executive of Johnson & Johnson, told lawmakers the company had "let the public down" by not maintaining high quality control standards.

"We are working hard to restore the public's trust and confidence in Johnson & Johnson and to strive to ensure that something like this never happens, ever again," Weldon said.

By the end of 2010, the recalls had cost McNeil approximately $900 million in sales, it reported. Many Tylenol products vanished from the shelves for months. The company recently acknowledged that it faces federal investigations related to the recalls; it said it is cooperating with the probes. The company's Fort Washington plant remains closed.

Meanwhile, McNeil has faced new court challenges about the risks of its billion-dollar brand.

In the past few years, about 100 lawsuits have been filed, contending that McNeil has failed to adequately warn the public about the true danger of Tylenol. Most of the lawsuits have been consolidated before a federal judge in Philadelphia. McNeil is fighting the claims, saying its warnings were adequate. Many of the cases allege that consumers suffered injury or death after taking Tylenol at or near the maximum recommended daily dose.

After enduring all the negative headlines about its manufacturing plant, getting hit with scores of lawsuits, and even being removed from some markets for months, Tylenol retains its power as a brand — a testament to the decades of skillful marketing.

In Johnson & Johnson's July earnings call, top officials said McNeil's over-the-counter revenue had surged by 26 percent. Children's Tylenol was one of the top two brands in over-the-counter pediatric pain relief.

And the company's flagship product? Extra Strength Tylenol had doubled its market share in the first half of 2013.

Once again, it was America's No. 1 over-the-counter adult pain medicine.